Excerpt from Transcript of Oral Argument Before the Honorable Ricardo M. Urbina, *Mylan Pharms., Inc. v. Donna Shalala, et al.*, (Docket No. CA 00-2876) (D.D.C.), dated Jan. 24, 2001.

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UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

Mylan Pharmaceuticals, Inc. Plaintiff vs. Donna S. Shalala, et al. Defendants	Docket No. CA 00-2876 RMU Washington, D.C. Wednesday, January 24, 2001 10:10 a.m.

Transcript of Oral Argument
Before the Honorable Ricardo M. Urbina
United States District Judge

APPEARANCES:

For the Plaintiff: Steven Lieberman, Esq.
Anthony Figg, Esq.
Elizabeth Leff, Esq.

For the Defendant: Andrew E. Clark, Esq.
Kevin Fain, Esq.
Evan R. Chesler, Esq.
J. Daniel Kiser, Esq.
Matthew D. Peterson, Esq.
Richard J. Stark, Esq.
David Marriott, Esq.

Reporter: WILLIAM D. MC ALLISTER, CVR-CM
Official Court Reporter
Room 4806-B
333 Constitution Avenue, N.W.
Washington, D.C. 20001-8306
(202) 371-6446

[Portions omitted.]

We are looking forward to hearing that answer. It does not show up anywhere in Bristol's briefs and we think the reason it does not show up is because they do not have an answer.

With respect to question 5, Your Honor has quoted from the Bristol brief one of those words that Bristol has used to suggest to the court that it is taking on an enormous burden if it deals with the improper listing issue here, a panoply of procedures and issue determinations involved in traditional patent litigation.

Your Honor doesn't have to deal with the panoply of patent infringement issues. First of all, there is no issue here of invalidity or enforceability. The only issue is claim construction. There is no issue here of infringement. As Your Honor knows from the Canady case and I assume other cases, there are two questions involved when you look at the issue of patent infringement. The first step is the legal issue of construing the claim language to see what it means. The second is the factual issue of applying that construed language to an accused product.

Here only the first issue is implicated construing the claims. Mylan's product is not at issue here. Mylan's product would be at issue in a patent infringement litigation. What is at issue here is whether BuSpar, Bristol's product under the statute, meets those two tests set out in 355(c)(2) and as to whether or not there could be any factual issue regarding whether or not, properly construed, the claim covers an approved use of buspirone.

[Portions Omitted]

The test under 355(c)(2) is, does the patent cover a method of using the approved product, BuSpar, and could a claim of patent infringement reasonably be asserted against one who made, used or sold that drug without a license.

This is the way the FDA has interpreted this provision over the years, and I would ask you if Your Honor has any questions about that to ask Mr. Clark to check with his colleagues and to provide a written submission to the court on this. That is the way this provision has always been interpreted and applied, and we suggest that is the only way that statutory section can be read.

The reason this is so important is because Mr. Chesler keeps talking about the overlap between the patent infringement actions in other jurisdictions and what's before this court. What is before this court is claim construction and then the question whether 355(c)(2) can be satisfied. That has nothing whatsoever to do with whether the Mylan product infringes or would infringe the '365 patent. The statutory question is a very important one.

[Portions omitted.]

**Compl., *Mylan Pharms., Inc. v. Bristol-Myers Squibb Co.*,
(Civil Action No. 1:00-CV-205) (N.D. W. Va.),
dated Nov. 28, 2000.**

IN THE UNITED STATES DISTRICT COURT
NORTHERN DISTRICT OF WEST VIRGINIA

MYLAN PHARMACEUTICALS INC. 781 Chestnut Ridge Road, Morgantown, West Virginia 26505, Plaintiff, v. BRISTOL-MYERS SQUIBB CO., 345 Park Avenue New York, New York, 10154, Defendant.	Civil Action No. 1:00-CV-205

COMPLAINT FOR DECLARATORY JUDGMENT

Plaintiff, Mylan Pharmaceuticals Inc. ("Mylan"), by and through its undersigned counsel, files this Complaint for Declaratory Judgment against Defendant, Bristol-Myers Squibb Co. ("BMS"), averring as follows:

NATURE OF THE ACTION

1. This is an action for a declaratory judgment pursuant to 28 U.S.C. §§ 2201 and 2202. This action arises under the Patent Laws of the United States, in particular 35 U.S.C. §§ 102, 103, 112 and 271.

THE PARTIES

2. Mylan is a corporation organized and existing under the laws of the State of West Virginia and has its principal

place of business at 781 Chestnut Ridge Road, Morgantown, West Virginia. Mylan has long been engaged in the research, development, manufacturing, and distribution of generic pharmaceutical products.

3. Upon information and belief, BMS is a corporation organized under the laws of the State of Delaware, having an office and principal place of business at 345 Park Avenue, New York, New York, 10154. Upon information and belief, BM S is the assignee of U.S. Patent 6,150,365 the "'365 patent") entitled Anxiety Method, a copy of which is annexed hereto as Exhibit 1.

JURISDICTION AND VENUE

4. This court has jurisdiction over the subject matter of this action under 28 U.S.C. § 1338(a).

5. Venue is proper in this district court pursuant to 28 U.S.C. §§ 1391(b) and (c).

6. Upon information and belief, this Court has personal jurisdiction over Defendants.

7. Mylan has filed an abbreviated new drug application ("ANDA"), No. 75-272, under Section 505(j) of the Federal Food, Drug and Cosmetic Act seeking approval to engage in the commercial manufacture, use and sale of its pharmaceutical formulation containing buspirone hydrochloride as a generic version of a product marketed by BMS under the trademark BUSPAR®.

8. The United States Food and Drug Administration (the "FDA") has tentatively approved Mylan's ANDA to market its buspirone hydrochloride product, evincing the Agency's determination that Mylan's ANDA meets all substantive safety

and efficacy requirements. Upon information and belief, the FDA was prepared to grant final approval of Mylan's ANDA with respect to its 15 mg buspirone hydrochloride tablet (the "Mylan Buspirone Product") no later than November 22, 2000.

9. Upon information and belief, the only reason that the FDA has not granted final approval with respect to Mylan's Buspirone Product is that, as discussed below, on November 21, 2000, BMS filed a copy of the '365 patent with the FDA and requested its listing in the Orange Book.

10. Mylan has been and remains prepared to commence marketing, sale and shipment of its Buspirone product immediately upon receipt of FDA final approval. Mylan has an inventory of its Buspirone Product ready for sale and has advertised the imminent availability of the product for purchase. Mylan plans to commence sale and shipment of its Buspirone Product immediately upon receipt of the FDA's final approval of Mylan's ANDA.

11. BMS has enjoyed market exclusivity with regard to buspirone since the launch of its BUSPAR® product in 1986, by virtue of two patents of which it is the assignee. United States Patent 4,182,763 ("the '763 patent") issued on January 8, 1980 and was granted two years of term extension to compensate for the lost benefit of patent term consumed by delays in regulatory approval of BUSPAR®, and BMS received a further six months of non-patent exclusivity under 21 U.S.C. § 355(a) for submitting data to support an indication for pediatric use. The market exclusivity that BMS has enjoyed from the '763 patent expired at midnight on November 22, 2000. BMS has also been accorded market exclusivity with regard to a second patent, U.S. Patent No. 5,015,646 ("the '646 patent"), covering a specific polymorphic form of buspirone. The period of exclusivity associated with the '646 patent is due to expire on May 14, 2008.

12. The '763 and the '646 patents are both listed in the FDA publication "Approved Drug Products" (commonly known as the "Orange Book") as patents as to which a reasonable claim of patent infringement could be asserted if a person not licensed by BMS engaged in the manufacture, use or sale of its approved buspirone hydrochloride product. Because they are listed in the Orange Book, Mylan was required to file with the FDA, as part of its ANDA, certifications under 21 U.S.C. 355(j)(2)(A)(vii) with respect to the '646 and '763 patents. With respect to the '646 patent, Mylan certified under § 355(j)(2)(A)(vii)(IV) that the patent would not be infringed by the commercial manufacture, use or sale of Mylan's buspirone hydrochloride product. This so-called "paragraph IV" certification, coupled with notice to the patent owner, creates an automatic stay of final approval for 45 days, after which, if no charge of infringement has been brought against the ANDA applicant by the patent owner, final approval can be granted. With respect to the '763 patent, Mylan filed a certification under § 355(j)(2)(A)(vii)(III), stating the date on which the patent would expire. Pursuant to this "paragraph III" certification, final approval can be granted upon the expiration of the patent. Because BMS did not sue Mylan for infringement of the '646 patent, approval of Mylan's ANDA could become final on November 22, 2000, after expiration of the '763 patent and upon expiration of all regulatory exclusivities.

13. On November 21, 2000, the United States Patent and Trademark Office issued the '365 patent, which is assigned on its face to BMS. That same day, BMS hand-delivered a request to the U.S. Food and Drug Administration that the '365 patent be listed in the Orange Book as a patent as to which a reasonable claim of patent infringement could be asserted if a person not licensed by BMS engaged in the manufacture, use or sale of its approved buspirone hydrochloride product.

14. The '365 patent contains one claim, which reads as follows:

> 1. A process for ameliorating an undesirable anxiety state in a mammal comprising systemic administration to the mammal of an effective but non-toxic anxiolytic dose of 6-hydroxy-8-[4-[4-(2-pyrimidinyl)-piperazinyl]-butyl]-8-azaspiro[4.5]-7,9-dione or a pharmaceutically acceptable acid addition salt or hydrate thereof.

The compound recited in the claim, 6-hydroxy-8-[4-[4-(2-pyrimidinyl)-piperazinyl]-butyl]-8-azaspiro[4.5]-7,9-dione, is a known metabolite of buspirone.

15. As a direct result of the listing of the '365 patent, FDA has declined to issue to Mylan the expected final approval of its ANDA.

16. Thus, the only thing standing between Mylan's marketing its Buspirone Product is this Court's determination of the infringement and validity of claim 1 of the '365 patent.

17. BMS has placed Mylan in reasonable apprehension that it will be sued for the alleged infringement of the '365 patent when Mylan launches its Buspirone Product. Upon information and belief, BMS informed the FDA at the time it requested listing of the '365 patent, that this patent covered all uses of buspirone. During the prosecution of the '365 patent, BMS petitioned the U.S. Patent and Trademark Office to expedite issuance of the '365 patent, stating

> The allowed claim of the application covers an active metabolite of the anti-anxiety drug Buspirone. This product is extremely important to the business of assignee of this application.... In order to maintain its

> product position in what becomes a highly competitive market, assignee requires issuance of this patent prior to November 22, 2000. (Emphasis in original.)

On November 27, 2000, BMS sent a letter to Mylan referencing the '365 patent and providing special delivery instructions with respect to any patent certification made with respect thereto. These statements, coupled with the listing of the patent in the Orange Book itself, evince a clear intention on the part of BMS to enforce this patent against Mylan.

18. At this point in time the '365 patent is the only impediment to Mylan's sale of its Buspirone Product. Mylan has buspirone product in waiting and is ready, willing and able to ship it immediately upon receipt of FDA approval. Therefore, there exists a substantial and continuing controversy between Mylan and BMS as to the validity and infringement of the '365 patent.

COUNT 1: DECLARATORY JUDGMENT OF PATENT NO INFRINGEMENT

19. Mylan repeats and realleges the allegations of paragraphs 1-18 as if set forth herein.

20. Mylan's 5, 10, and 15 mg buspirone hydrochloride products do not contain an anxiolytically effective dose of 6-hydroxy-8-[4-[4-(2-pyrimidinyl)-piperazinyl]-butyl]-8-azaspiro[4.5]-7,9-dione.

21. Mylan's sale of its 5, 10, and 15 mg buspirone hydrochloride products will not infringe or contribute to infringement of the '365 patent.

22. Mylan will not induce others to infringe the '365 patent because the use of Mylan's product according to label

directions will not fall within the scope of the claim of the '365 patent, and therefore does not infringe any such claim.

COUNT 2: DECLARATORY JUDGMENT OF PATENT VALIDITY

23. Mylan repeats and realleges the allegations of paragraphs 1-22 as if set forth herein.

24. The claims of the '365 patent are invalid under one or more of 35 U.S.C. §§ 101, 102, 103 and/or 112.

WHEREFORE, Mylan respectfully request that this Court enter the following relief:

A. a declaratory judgment that the Mylan is not liable for infringement of the '365 patent;

B. a declaratory judgment that the '365 patent is invalid;

C. an order directing the FDA immediately to grant final approval of Mylan's ANDA 75-272;

D. a declaration that this case is exceptional under 35 U.S.C. § 285;

E. a judgment in favor of Mylan for its attorneys fees, costs, and expenses in this action; and

F. a judgment in favor of Mylan for such further necessary proper relief as this court may deem just and proper.

Dated: November 28, 2000 Respectfully submitted,

By: /s/

Gordon Copland
(WV Bar No. 828)
Megan Dortenzo
(WV Bar No. 7264)
STEPTOE & JOHNSON
P.O. Box 2190
Clarksburg, WV 26301
304-624-8000

Attorneys for Plaintiff Mylan Pharmaceuticals Inc.

Of Counsel:

E. Anthony Figg
Steven Lieberman
Elizabeth A. Leff
Mark I. Bowditch
ROTHWELL, FIGG, ERNST
& MANBECK, P. C.
Suite 701-E; 555 13th St., N.W.
Washington, DC 20004
(202) 783-6040

Letter from R. Temple to F. Furth,
dated Sept. 29, 1986.

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DEPARTMENT OF HEALTH & HUMAN SERVICES

NDA 18-731

[Sept. 29, 1986]

Bristol-Myers Company
Attention: Frank Furth, M.D.
5 Research Parkway
P.O. Box 5100
Wallingford, Connecticut 06492-7660

Dear Dr. Furth:

Please refer to your new drug application dated December 18, 1982 submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for the preparation BuSpar® (buspirone hydrochloride) tablets, NDA 18-731.

We also acknowledge receipt of your additional communications dated:

July 9, 1986	August 28, 1986
July 22, 1986	September 2, 1986
August 5, 1986	September 2, 1986
August 19, 1986	September 3, 1986
August 20, 1986	September 4, 1986
August 22, 1986	September 5, 1986
August 28, 1986	

We have completed the review of this application and have concluded that adequate information has been presented to demonstrate that buspirone is safe and effective for use as recommended in the revised labeling that was developed at our meeting of August 29, 1986 and in subsequent telephone conversations. The application is approved effective as of the

date of this letter. The Final Printed Labeling (FPL) must be identical to that incorporated in the body of this letter. Marketing the product with FPL that is not identical to that labeling may render the product misbranded and an unapproved new drug. Please submit twelve copies of the FPL (including container and package labeling) to the FDA as soon as available. For administrative purposes this submission should be designated "FPL Supplement" to the approved NDA. Approval of this supplement by the FDA is not required before the labeling is used.

In addition to the submission of revised labeling, the approval of the application is conditioned upon your commitment, made earlier, to conduct a Phase IV post-marketing study to determine to what degree prior exposure to benzodiazepine treatment affects the clinical efficacy of BuSpar®.

With regard to biopharmaceutical requirements, we acknowledge your agreement to conduct 1) an appropriate Phase IV multiple dose bioavailability study comparing the 5 mg and 10 mg ovoid-rectangular (pillow-shaped) tablets and a reference oral solution, and 2) an appropriate in vitro protein binding study to determine the effect of highly protein bound drugs on the protein binding of buspirone. The Division of Biopharmaceutics has agreed to lower the dissolution specification from Q = 85% to Q = 80% in 30 minutes. Finally, the Division of Biopharmaceutics agrees with your decision to include bioavailability data for the pillow-shaped tablets rather than that of the round tablets in the labeling, provided that you agree to update the bioavailability/pharmacokinetic information in the labeling when the Phase IV steady state bioavailability study is completed.

The approved labeling of BuSpar® follows:

Final Labeling:
September 15, 1986

BuSpar® tablets (buspirone hydrochloride)

DESCRIPTION:

BuSpar® (buspirone hydrochloride) is an antianxiety agent that is not chemically or pharmacologically related to the benzodiazepines, barbiturates, or other sedative/anxiolytic drugs.

BuSpar® is a white crystalline, water soluble compound with a molecular weight of 422.0. Chemically, BuSpar® is 8-[4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl]-8-a zaspiro[4 .5] decane-7,9-dione monohydrochloride. The empirical formula $C_{21}H_{31}N_5O_2$ HCl is represented by the following structural formula:

[Formula].

BuSpar® is supplied for oral administration in 5mg and 10mg white, ovoid-rectangular, scored tablets. BuSpar® tablets, 5mg and 10 mg, contain the following inactive ingredients: colloidal silicon dioxide, lactose, magnesium stearate, microcrystalline cellulose, and sodium starch glycolate.

CLINICAL PHARMACOLOGY:

The mechanism of action of BuSpar® is unknown. BuSpar® differs from typical benzodiazepine anxiolytics in that it does not exert anticonvulsant or muscle relaxant effects. It also lacks the prominent sedative effect that is associated with more typical anxiolytics. In vitro preclinical studies have shown that

buspirone has a high affinity for serotonin-1A (5-HT_{1A}) receptors. BuSpar® has no significant affinity for benzodiazepine receptors and does not affect GABA binding in vitro or in vivo when tested in preclinical models.

BuSpar® has moderate affinity for D_2 dopamine receptors. Some studies suggest that BuSpar® may have indirect effects on other neurotransmitter systems.

BuSpar® is rapidly absorbed in man and undergoes extensive first pass metabolism. In a radiolabeled study, unchanged BuSpar® in the plasma accounted for only about 1% of the radioactivity in the plasma. Following oral administration, plasma concentrations of unchanged BuSpar® are very low and variable between subjects. Peak plasma levels of 1 to 6 ng/ml have been observed 40 to 90 minutes after single oral doses of 20 mg. The single dose bioavailability of unchanged BuSpar® when taken as a tablet is on the average about 90% of an equivalent dose of solution, but there is large variability.

The effects of food upon the bioavailability of BuSpar® have been studied in eight subjects. They were given a 20 mg dose with and without food; the area under the plasma concentration-time curve (AUC) and peak plasma concentration (Cmax) of unchanged BuSpar® increased by 84% and 116% respectively, but the total amount of buspirone immuno-reactive material did not change. This suggests that food may decrease the extent of presystemic clearance of BuSpar®, but the clinical significance of these findings is unknown.

A multiple dose study conducted in fifteen subjects suggests that BuSpar® has nonlinear pharmacokinetics. Thus, dose increases and repeated dosing may lead to somewhat higher blood levels of unchanged buspirone than would be predicted from results of single dose studies.

In man, approximately 95% of BuSpar® is plasma protein bound, but other highly bound drugs, e.g., phenytoin, propranolol and warfarin are not displaced by BuSpar® from plasma protein in vitro. However, in vitro binding studies show that BuSpar® does displace digoxin.

BuSpar® is metabolized primarily by oxidation producing several hydroxylated derivatives and a pharmacologically active metabolite, 1-pyrimidinyl piperazine (1-PP). In animal models predictive of anxiolytic potential, 1-PP has about one quarter of the activity of BuSpar®, but is present in up to 20 fold greater amounts. However, this is probably not important in humans: blood samples from humans chronically exposed to BuSpar® do not exhibit high levels of 1-PP; mean values are approximately 3ng/ml and the highest human blood level recorded among 108 chronically dosed patients was 17ng/ml, less than 1/200th of 1-PP levels found in animals given large doses of BuSpar® without signs of toxicity.

In a single dose study using ^{14}C labeled BuSpar®, 29 to 63% of the dose was excreted in the urine within 24 hours, primarily as metabolites; fecal excretion accounted for 18 to 38% of the dose. The average elimination half-life of unchanged BuSpar® after single doses of 10 to 40 mg is about 2 to 3 hours.

The pharmacokinetics of BuSpar® in patients with hepatic or renal dysfunction have not been determined, nor has the effect of age. The effect of BuSpar® on drug metabolism or concomitant drug disposition has not been investigated.

INDICATIONS AND USAGE:

BuSpar® is indicated for the management of anxiety disorders or the short term relief of the symptoms of anxiety. Anxiety or tension associated with the stress of every day life usually does not require treatment with an anxiolytic.

The efficacy of BuSpar® has been demonstrated in controlled clinical trials of outpatients whose diagnosis roughly corresponds to Generalized Anxiety Disorder (300.02) of the American Psychiatric Association's Diagnostic and Statistical Manual, III[1] as described below:

> Generalized, persistent anxiety (of at least one month continual duration), manifested by symptoms from three of the four following categories.
>
> 1. Motor tension: shakiness, jitteriness, jumpiness, trembling, tension, muscle aches, fatigability, inability to relax, eyelid twitch, furrowed brow, strained face, fidgeting, restlessness, easy startle.
>
> 2. Autonomic hyperactivity: sweating, heart pounding or racing, cold, clammy hands, dry mouth, dizziness, light-headedness, paresthesias (tingling in hands or feet), upset stomach, hot or cold spells, frequent urination, diarrhea, discomfort in the pit of the stomach, lump in the throat, flushing, pallor, high resting pulse and respiration rate.
>
> 3. Apprehensive expectation: anxiety, worry, fear, rumination, and anticipation of misfortune to self or others.
>
> 4. Vigilance and scanning: hyperattentiveness resulting in distractibility, difficulty in concentrating, insomnia, feeling "on edge", irritability, impatience.

The above symptoms would not be due to another mental disorder, such as a depressive disorder or schizophrenia.

The effectiveness of BuSpar® in long term use, that is, for more than three to four weeks, has not been demonstrated in

controlled trials. However, patients have been treated with BuSpar® for several months without ill effect. Therefore, the physician who elects to use BuSpar® for extended periods should periodically reassess the usefulness of the drug for the individual patient.

CONTRAINDICATIONS:

BuSpar® is contraindicated in patients hypersensitive to buspirone hydrochloride.

WARNINGS:

Because BuSpar® has no established antipsychotic activity, it should not be employed in lieu of appropriate antipsychotic treatment.

PRECAUTIONS:

General:

Interference with Cognitive and Motor Performance:

Studies indicate that BuSpar® is less sedating than other anxiolytics and that it does not produce significant functional impairment. However, its CNS effects in any individual patient may not be predictable. Therefore, patients should be cautioned about operating an automobile or using complex machinery until they are reasonably certain that buspirone treatment does not affect them adversely.

While formal studies of the interaction of BuSpar® with alcohol indicate that buspirone does not increase alcohol induced impairment in motor and mental performance, it is prudent to avoid concomitant use of alcohol and buspirone.

Potential for Withdrawal Reactions in Sedative/Hypnotic/ Anxiolytic Drug Dependent Patients:

Because BuSpar® does not exhibit cross-tolerance with benzodiazepines and other common sedative/hypnotic drugs, it will not block the withdrawal syndrome often seen with cessation of therapy with these drugs. Therefore, before starting therapy with BuSpar®, it is advisable to withdraw patients gradually, especially patients who have been using a CNS depressant drug chronically, from their prior treatment. Rebound or withdrawal symptoms may occur over varying time periods, depending in part on the type of drug, and its effective half-life of elimination.

The syndrome of withdrawal from sedative/hypnotic/ anxiolytic drugs can appear as any combination of irritability, anxiety, agitation, insomnia, tremor, abdominal cramps, muscle cramps, vomiting, sweating, flu-like symptoms without fever, are, occasionally, even as seizures.

Possible Concerns Related to Buspirone's Binding to Dopamine Receptors:

Because buspirone can bind to central dopamine receptors, a question has been raised about its potential to cause acute and chronic changes in dopamine mediated neurological function (e.g., dystonia, pseudo-parkinsonism, akathisia, and tardive dyskinesia). Clinical experience in controlled trials has failed to identify any significant neuroleptic-like activity; however, a syndrome of restlessness, appearing shortly after initiation of treatment, has been reported in some small fraction of buspirone treated patients. The syndrome may be explained in several ways. For example, buspirone may increase central noradrenergic activity; alternatively, the effect may be attributable to dopaminergic effects (i.e., represent akathisia). Obviously, the question cannot be totally resolved at this point

in time. Generally, long-term sequelae of any drug's use can be identified only after several years of marketing.

Information for Patients:

To assure safe and effective use of BuSpar®, the following information and instructions should be given to patients:

1. Inform your physician about any medications, prescription or non-prescription, alcohol or drugs that you are now taking or plan to take during your treatment with BuSpar®.

2. Inform your physician if you are pregnant, or if you are planning to become pregnant, or if you become pregnant while you are taking BuSpar®.

3. Inform your physician if you are breast feeding an infant.

4. Until you experience how this medication affects you, do not drive a car or operate potentially dangerous machinery.

Laboratory Tests:

There are no specific laboratory tests recommended.

Drug Interactions:

Because the effects of concomitant administration of BuSpar® with most other psychotropic drugs have not been studied, the concomitant use of BuSpar® with other CNS active drugs should be approached with caution.

There is one report suggesting that the concomitant use of Desyrel (trazodone) and BuSpar® may have caused 3 to 6 fold

elevations in SGPT (ALT) in a few patients. In a similar study, attempting to replicate this finding, no interactive effect on hepatic transaminases was identified.

BuSpar® does not displace tightly bound drugs like phenytoin, propranolol and warfarin from serum proteins. However, it may displace less firmly bound drugs like digoxin; the clinical significance of this property is unknown.

Drug Laboratory Interactions:

BuSpar® is not known to interfere with commonly employed clinical laboratory tests.

Carcinogenesis, Mutagenesis, Impairment of Fertility:

No evidence of carcinogenic potential was observed in rats during a 24-month study at approximately 133 times the maximum recommended human oral dose; or in mice, during an 18-month study at approximately 167 times the maximum recommended human oral dose.

With or without metabolic activation, BuSpar® did not induce point mutations in 5 strains of Salmonella typhimurium (Ames Test) or mouse lymphoma L5178YTK^{+} cell cultures, nor was DNA damage observed with BuSpar® in Wi-38 human cells. Chromosomal aberrations or abnormalities did not occur in bone marrow cells of mice given one or five daily doses of BuSpar®.

Pregnancy: Teratogenic Effects:

Pregnancy Category B: No fertility impairment or fetal damage was observed in reproduction studies performed in rats and rabbits at BuSpar® doses of approximately 30 times the maximum recommended human dose. In humans, however, adequate and well controlled studies during pregnancy have not

been performed. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery:

The effect of BuSpar® on labor and delivery in women is unknown. No adverse effects were noted in reproduction studies in rats.

Nursing Mothers:

The extent of the excretion in human milk of BuSpar® or its metabolites is not known. In rats, however, BuSpar® and its metabolites are excreted in milk. BuSpar® administration to nursing women should be avoided if clinically possible.

Pediatric Use:

The safety and effectiveness of BuSpar® has not been determined in individuals below 18 years of age.

Use in the Elderly:

BuSpar® has not been systematically evaluated in older patients; however, several hundred elderly patients have participated in clinical studies with BuSpar®, and no unusual adverse age related phenomena have been identified. In 87 elderly patients for whom dosage data were available, the modal total daily dose of BuSpar® was 15 mg/day, the same as that in the total sample of patients treated with BuSpar®.

Use in Patients with Impaired Hepatic or Renal Function:

Since BuSpar® is metabolized by the liver and excreted by the kidneys, its administration to patients with severe hepatic or renal impairment cannot be recommended.

ADVERSE REACTIONS (See also PRECAUTIONS):

Commonly Observed:

The more commonly observed untoward events associated with the use of BuSpar® not seen at an equivalent incidence among placebo treated patients include dizziness, nausea, headache, nervousness, lightheadedness, excitement.

Associated with Discontinuation of Treatment:

One guide to the relative clinical importance of adverse events associated with BuSpar® is provided by the frequency with which they caused drug discontinuation during clinical testing. Approximately ten percent of the 2200 anxious patents who participated in BuSpar®'s premarketing controlled clinical trials, lasting three to four weeks, discontinued treatment due to an adverse event.

The more common events causing discontinuation included: central nervous system disturbances (3.4%), primarily dizziness, insomnia, nervousness, drowsiness and lightheaded feeling; gastrointestinal disturbances (1.2%), primarily nausea; and miscellaneous disturbances (1.1%), primarily headache and fatigue. In addition, 3.4% of patients had multiple complaints, none of which could be characterized as primary.

Incidence in Controlled Clinical Trials:

The table that follows enumerates adverse events that occurred at a frequency of 1% or more among BuSpar® patients who participated in four week, controlled trials comparing BuSpar® with placebo. The frequencies were obtained from pooled data for seventeen trials. The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses and investigators. Comparison of the cited figures, however, does provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the side effect incidence rate in the population studied.

Treatment Emergent Adverse Experience Incidence
in Placebo-Controlled Clinical Trials*
(Percent of Patients Reporting)

Adverse Experience	BuSpar® (n=477)	Placebo (n=464)
Cardiovascular		
Tachycardia/Palpitations	1	1
CNS		
Dizziness	12	3
Drowsiness	10	9
Nervousness	5	1
Insomnia	3	3
Lightheadedness	3	-
Decreased Concentration	2	2
Excitement	2	-
Anger/Hostility	2	-
Confusion	2	-

Depression	2	2
EENT		
Blurred Vision	2	-
Gastrointestinal		
Nausea	8	5
Dry Mouth	3	4
Abdominal/Gastric Distress	2	2
Diarrhea	2	-
Constipation	1	2
Vomiting	1	2
Musculoskeletal		
Musculoskeletal Aches/Pains	1	-
Neurological		
Numbness	2	-
Paresthesia	1	-
Incoordination	1	-
Tremor	1	-
Skin		
Skin Rash	1	-
Miscellaneous		
Headache	6	3
Fatigue	4	4
Weakness	2	-
Sweating/Clamminess	1	-

(*) Events reported by at least 1% of BuSpar® patients are included.
(-) Incidence less than 1%.

Other Events Observed During the Entire Premarketing Evaluation of BuSpar:

During its premarketing assessment, BuSpar® was evaluated in over 3500 subjects. This section reports event frequencies for adverse events occurring in approximately 3000 subjects from this group who took multiple doses of BuSpar® in the dose range for which BuSpar® is recommended (i.e., the modal daily dose of BuSpar® fell between 10 and 30 mg for 70% of the patients studied) and for whom safety data were systematically collected. The conditions and duration of exposure to BuSpar® varied greatly, involving well-controlled studies as well as experience in open and uncontrolled clinical settings. As part of the total experience gained in clinical studies, various adverse events were reported. In the absence of appropriate controls in some of the studies, a causal relationship to BuSpar® treatment cannot be determined. The list includes all undesirable events reasonably associated with the use of the drug.

The following enumeration by organ system describes events in terms of their relative frequency of reporting in this data base. Events of major clinical importance are also described in the PRECAUTIONS section.

The following definitions of frequency are used: Frequent adverse events are defined as those occurring in at least 1/100 patients. Infrequent adverse events are those occurring in 1/100 to 1/1000 patients, while rare events are those occurring in less than 1/1000 patients.

Cardiovascular: Frequent was nonspecific chest pain; infrequent were syncope, hypotension and hypertension, rare were cerebrovascular accident, congestive heart failure, myocardial infarction, cardiomyopathy and bradycardia.

Central Nervous System: Frequent were dream disturbances; infrequent were depersonalization, dysphoria, noise intolerance, euphoria, akathisia, fearfulness, loss of interest, dissociative reaction, hallucinations, suicidal ideation and seizures; rare were

feelings of claustrophobia, cold intolerance, stupor, slurred speech and psychosis.

EENT: Frequent mere tinnitus, sore throat, and nasal congestion. Infrequent were redness and itching of the eyes, altered taste, altered smell, and conjunctivitis; rare were inner ear "'abnormality", eye pain, photophobia, and pressure on eyes.

Endocrine: Rare were galactorrhea and thyroid abnormality.

Gastrointestinal: Infrequent were flatulence, anorexia, increased appetite, salivation, irritable colon and rectal bleeding; rare was burning of the tongue.

Genitourinary: Infrequent were urinary frequency, urinary hesitancy, menstrual irregularity and spotting, and dysuria; rare were amenorrhea, pelvic inflammatory disease, enuresis and nocturia.

Musculoskeletal: Infrequent were muscle cramps, muscle spasms, rigid/stiff muscles, and arthralgias.

Neurological: Infrequent were involuntary movements and slowed reaction time; rare was muscle weakness.

Respiratory: Infrequent were hyperventilation, shortness of breath and chest congestion; rare was epistaxis.

Sexual Function: Infrequent were decreased or increased libido; rare were delayed ejaculation and impotence.

Skin: Infrequent were edema, pruritus, flushing, easy bruising, hair loss, dry skin, facial edema and blisters; rare were acne, and thinning of nails.

Clinical Laboratory: Infrequent were increases in hepatic aminotransferases (SGOT, SGPT); rare were eosinophilia, leukopenia and thrombocytopenia.

Miscellaneous: Infrequent were, weight gain, fever, roaring sensation in the head, weight loss and malaise; rare were alcohol abuse, bleeding disturbance, loss of voice and hiccoughs.

NON-DOMESTIC POST-MARKETING EXPERIENCE:

Foreign post-marketing experience has shown an adverse experience profile similar to that given above and no other unexpected adverse reactions have been reported to date.

DRUG ABUSE AND DEPENDENCE:

Controlled Substance Class:

BuSpar® is not a controlled substance.

Physical and Psychological Dependence:

In human and animal studies; BuSpar® has shown no potential for abuse or diversion and there is no evidence that it causes tolerance, or either physical or psychological dependence. Human volunteers with a history of recreational drug or alcohol usage were studied in two double-blind clinical investigations. None of the subjects were able to distinguish between BuSpar® and placebo. By contrast, subjects showed a statistically significant preference for methaqualone and diazepam. Studies in monkeys, mice, and rats have indicated that BuSpar® lacks potential for abuse.

Following chronic administration in the rat, abrupt withdrawal of BuSpar® did not result in the loss of body weight commonly observed with substances that cause physical dependency.

Although there is no direct evidence that BuSpar® causes physical dependence or drug seeking behavior, it is difficult to predict from experiments the extent to which a CNS active drug will be misused, diverted and/or abused once marketed. Consequently, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of BuSpar® misuse or abuse (e.g., development of tolerance, incrementation of close, drug seeking behavior).

OVERDOSAGE:

Signs and Symptoms:

In clinical pharmacology trials, doses as high as 375 mg a day were administered to healthy male volunteers. As this dose was approached, the following signs were observed: nausea, vomiting, dizziness, drowsiness, miosis, and gastric distress. No deaths have been reported in humans either with deliberate or accidental overdosage of BuSpar®. Toxicology studies of BuSpar® yielded the following LD_{50} values: mice, 655 mg/kg; rats, 196 mg/kg; dogs, 586 mg/kg; and monkeys, 356 mg/kg. These dosages are 160-550 times the recommended human daily dose.

Recommended Overdose Treatment:

General symptomatic and supportive measures should be used along with immediate gastric lavage. Respiration, pulse, and blood pressure should be monitored as in all cases of drug overdosage. No specific antidote is known to BuSpar®, and dialyzability of BuSpar® has not been determined.

DOSAGE AND ADMINISTRATION:

The recommended initial dose is 15 mg daily (5 mg three times a day). To achieve an optimal therapeutic response, at intervals of 2 to 3 days the dosage may be increased 5 mg per day, as needed. The maximum daily dosage should not exceed 60 mg per day. In clinical trials allowing dose titration, divided doses of 20-30 mg per day were commonly employed.

HOW SUPPLIED:

BuSpar® (buspirone hydrochloride)

Tablets, 5 mg and 10 mg (white, ovoid-rectangular with score, MJ logo, strength and the name BuSpar® embossed) are available in bottles of 100.

NDC 0087-0818-41 5 mg tablet	Bottles of 100
NDC 0087-0819-41 10 mg tablet	Bottles of 100

Store at Room Temperature - Protect from Temperatures greater than 86°F (30°C).

REFERENCE

1. Williams, JWB, Ed.: Diagnostic and Statistical Manual of Mental Disorders-III, American Psychiatric Association, May 1980.

END OF TEXT

Should additional information relating to the safety and effectiveness of these drug products become available prior to our receipt of the final printed labeling, revision of the labeling may be required.

Please submit one market package of the drug when it is available.

We remind you that you must comply with the requirements set forth under 21 CFR 314.80 and 314.81 for an approved NDA.

Sincerely yours,

/s/

Robert Temple, M.D.
Director
Office of Drug Research and
Review Center for Drugs and
Biologics

Excerpt of Mem. Op., *Mylan Pharms., Inc. v. Thompson et al.*, (Civil Action No. 00-2876) (RMU) (D.D.C.), dated Mar. 14, 2001.

UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

MYLAN PHARMACEUTICALS, INC., Plaintiff, v. TOMMY G. THOMPSON, Secretary, United States Department of Health and Human Services, United States Food and Drug Administration, and BRISTOL-MYERS SQUIBB CO., Defendants.	Civil Action No.: 00-2876 (RMU) Document Nos.: 3, 4

MEMORANDUM OPINION

GRANTING THE PLAINTIFF'S REQUEST FOR A PRELIMINARY INJUNCTION

[Portions omitted.]

[Portions omitted.]

Mylan is the nation's largest generic drug manufacturer. *See* Bristol Opp'n at 1. On September 29, 1998, Mylan submitted an ANDA to the FDA for a generic version of buspirone tablets. *See* FDA Opp'n at 9. Mylan's ANDA contained a Paragraph III certification stating that it would not market its generic product until the expiration of Bristol's patent 4,182,763 ("the '763 patent"). *See id.* The FDA "tentatively approved" Mylan's ANDA, with final approval contingent only on the expiration of Bristol's exclusivity on November 22, 2000. *See i.d.*; Mot. for Prelim. Inj. at 2. Anticipating the expiration of Bristol's exclusivity, Mylan took the steps necessary to put its buspirone product on the market, even loading its trucks with generic buspirone tablets for shipment beginning at 12:00 a.m. on November 22, 2000. *See* Mot. for Prelim. Inj. at 2.

[Portions omitted.]

VI. CONCLUSION

For the foregoing reasons, the court orders as follows:

Defendant Bristol-Myers Squibb Co. is hereby enjoined to request that Defendant FDA delist U.S. Patent No. 6,150,365 from its publication "Approved Drug Products with Therapeutic Equivalence Evaluations" (also known as the "Orange Book"), that is, Bristol is directed to request the FDA to remove its '365 patent from the Orange Book; and

Defendant Tommy G. Thompson, the United States Food and Drug Administration, and their agents, servants and employees are hereby ordered to grant immediate approval of Mylan's abbreviated new drug application (ANDA) No. 75-272 to market its pharmaceutical product containing buspirone hydrochloride as a generic version of BuSpar®.

An Order directing the parties in a manner consistent with this Memorandum Opinion is separately and contemporaneously executed this [14] day of March 2001.

/s/
Ricardo M. Urbina
United States District Judge

Letter from G. Buehler to F.R. Sisto,
dated Aug. 2, 2000.

RA 35

DEPARTMENT OF HEALTH & HUMAN SERVICES

ANDA 75-272

Food and Drug Administration
Rockville, MD 20857

[August 2, 2000]

Mylan Pharmaceuticals Inc.
Attention: Frank R. Sisto
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26504-4310

Dear Sir:

This is in reference to your abbreviated new drug application dated September 29, 1998, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Buspirone Hydrochloride Tablets USP, 5 mg, 10 mg, and 15 mg.

Reference is also made to the tentative approval letter issued by this office on November 10, 1998, and to your amendments dated March 2, May 3, and May 25, 2000 requesting that final approval be made effective May 22, 2000.

We have completed the review of this abbreviated application as amended and have concluded that based upon the information you have presented to date, the drug product remains safe and effective for use as recommended in the submitted labeling. However, the application remains tentatively approved. This determination is based upon information available to the Agency at this time, (i.e., information in your application and the status of current good manufacturing practices (CGMPs) of the facilities used in the manufacture and testing of the drug

product), and is subject to change on the basis of new information that may come to our attention.

The reference listed drug product (RLD) upon which you have based your application, BuSpar® Tablets of Bristol Myers Squibb Co. Pharmaceutical Research Institute (BMS), is currently subject to periods of patent protection which were due to expire on May 22, 2000, (U.S. Patent No. 4,182,763, the '763 patent) and May 14, 2008, (U.S. Patent No. 5,015,646, the '646 patent). Your application contains a Paragraph IV Certification to the '646 patent under Section 505 (j) (2) (A) (vii) (IV) of the Act stating that your commercial manufacture, use, or sale of this drug product will not infringe on this patent. You have notified the Agency that Mylan Pharmaceuticals, Inc. (Mylan) has complied with the requirements of Section 505(j)(2)(B) of the Act and that no legal action regarding the '646 patent was brought against Mylan within the statutory forty-five day period. In addition, your application contains a Paragraph III Certification to the '763 patent under Section 505(j)(2)(A)(vii)(III) of the Act stating that you will not market this drug product prior to the expiration of this patent.

As noted in the current edition of the Agency's publication entitled "Approved Drug Products with Therapeutic Equivalence Evaluations", the "Orange Book", the '763 patent was scheduled to expire on May 22, 2000. However, Section 111 of Title I of the Food and Drug Administration Modernization Act of 1997 (the Modernization Act) created Section 505A of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355a). Section 505A permits the sponsor of the new drug application for the RLD to obtain an additional six months of exclusivity if, in accord with the statute, the sponsor submits data previously requested by the Agency relating to the safe and effective use of the drug in a pediatric population. In this case, the RLD holder, BMS, has submitted data to support the use of buspirone hydrochloride in a pediatric population. The agency's

Pediatric Exclusivity Board has determined that the data support the granting of 6 months of exclusivity to the RLD. Consequently, the awarding of this exclusivity will effectively lengthen the life of the two patents referenced above by an additional 6 months. Therefore, final approval of your application may not be made effective pursuant to 21 U.S.C. 355(j)(5)(B)(ii) of the Act until the additional exclusivity period granted to the RLD holder for the '763 patent has expired; i.e., November 22, 2000.

To reactivate your application, please submit an amendment at least 60 days (but not more than 90 days) prior to the date you believe your application will be eligible for final approval. This amendment should identify changes, if any, in the conditions under which the product was tentatively approved, and should include updated information such as final-printed labeling, chemistry, manufacturing, and controls data as appropriate. Please note that this amendment should be submitted even if none of these changes were made. The amendment should be designated clearly in your cover letter as a MINOR AMENDMENT. In addition to this amendment, the Agency may request at any time prior to the final date of approval that you submit an additional amendment containing the information described above.

Failure to submit such an amendment requested by the Agency will prompt a review of the application which may result in rescission of the tentative approval status of your application, or may result in a delay in the issuance of the final approval letter.

Any significant changes in the conditions outlined in this abbreviated application as well as changes in the status of the manufacturing and testing facilities' compliance with current good manufacturing practices (CGMPs) are subject to Agency review before final approval of the application will be made.

Please note that this drug product may not be marketed without final Agency approval under Section 505 of the Act. The introduction or delivery for introduction into interstate commerce of this drug product before the final approval date is prohibited under Section 501 of the Act and 21 U.S.C. 331(d). Also, until the Agency issues the final approval letter, this drug product will not be deemed approved for marketing under 21 U.S.C. 355 and will not be listed in the "Approved Drug Products with Therapeutic Equivalence Evaluations" list (the "Orange Book"), published by the Agency. Should you believe that there are grounds for issuing the final approval letter prior to November 22, 2000, you should amend your application accordingly.

At the time you submit any amendments, you should contact Ms. Elaine Hu, R.Ph., Project Manager, at (301) 827-5848, for further instructions.

Sincerely yours,

/s/

Gary Buehler
Acting Director
Office of
Generic Drugs
Center for Drug
Evaluation and
Research

Excerpt of letter from S. Manteleone to D.J. Barrack, dated Dec. 5, 2000.

RA 39

MYLAN TECHNOLOGIES INC.

December 5, 2000

Via Registered Mail --Return Receipt Requested

Office of the General Counsel
Bristol-Myers Squibb Company
Route 206 and Provinceline Road
Princeton, New Jersey 08540

Attention: Donald J. Barrack, Esq.
Senior Counsel, Patents

Re: Mylan Technologies Inc.
Notice of Paragraph IV Certification
U.S. Patent No. 6,150,365
Buspirone

Dear Sir or Madam:

Pursuant to 21 U.S.C. § 355(j)(2)(B)(ii) of the Federal Food, Drug and Cosmetic Act (the "Act"), 21 C.F.R. §§ 314.94 and 314.95, Mylan Technologies Inc. ("Applicant" or "Mylan") hereby provides the following information concerning U.S. Patent No. 6,150,365 (the "'365 patent"):

1. Applicant has submitted to the United States Food and Drug Administration ("FDA") an Abbreviated New Drug Application ("ANDA") which contains any required bioavailability or bioequivalence data or information, and which seeks approval to engage in the commercial manufacture, use and sale of buspirone hydrochloride tablet; oral ("Mylan's product") before the expiration date of the '365 patent.

2. The ANDA number is ANDA 76-008.

3. The established name as defined in § 352(e)(3) of the Act of the proposed drug product is "buspirone hydrochloride tablet; oral; 30mg."

4. The active ingredient of the proposed drug product is buspirone hydrochloride; the strength is 30mg, and the dosage form is a tablet.

5. The '365 patent was purportedly identified to the Food and Drug Administration ("FDA") pursuant to 21 U.S.C. § 355(b)(1)[1]. On information, Mylan believes that the patent's expiration date is August 5, 2019. No valid claim of the '365 patent will be infringed by the manufacture, use or sale of the product for which the application has been submitted by Applicant.

6. A detailed statement of the factual and legal bases of Applicant's opinion is set forth below.

[Portions omitted.]

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[1] Mylan is serving this notice letter as a result of the FDA's representation that the '365 patent was provisionally listed in the Orange Book; however, as set forth in papers recently filed by Mylan in the United States District Court for the District of Columbia (the content of which is incorporated herein by reference and copies of which have been served upon you), Mylan believes that this patent is not properly listed in the Orange Book.

CONCLUSION

For the foregoing reasons, the '365 patent will not be infringed, either literally or under the doctrine of equivalents, by the manufacture, use, sale or offer of sale Mylan's product. Further, if one were to construe the claim of '365 patent to encompass Mylan's product, then the claim would be invalid.

Mylan expressly reserves the right to challenge the validity and enforceability of the '365 patent and/or any assertion of infringement that Bristol-Myers Squibb might make on new, other or further grounds should such grounds become apparent during any ensuing litigation between the parties.

Sincerely,

/ s /

Shelly Monteleone, Esq.
Assistant Patent Counsel

Letter from M. Peterson to R. Lillie,
dated Dec. 4, 2000.

FOXKISER
750 17TH STREET, N.W.
SUITE 1100
WASHINGTON, D.C. 20006
(202) 778-2300

December 4, 2000

VIA FACSIMILE
Ralph Lillie, Director
Office of Information Technology
Center for Drug Evaluation and Research
Food and Drug Administration
Rockville MD 20857

RE: NDA 18-7311 for BuSpar®
(buspirone hydrochloride)

Dear Mr. Lillie:

This letter responds to your letter of November 30, 2000, to Michael S. Eison, Ph.D., of Bristol-Myers Squibb (BMS). In that letter you requested BMS to submit additional information on U.S. Patent No. 6,150,365 (the '365 patent) by December 6, 2000. Your letter indicates that your request was prompted by the complaints of applicants seeking approval of abbreviated new drug applications (ANDAs) for buspirone hydrochloride.

I. The Listing of the '365 Patent

As it was required to do by statute and FDA's regulations, BMS submitted information on the '365 patent to FDA on November 21, 2000. The '365 patent information submission complied in all respects with BMS's legal obligations: it

contained the patent number, date of expiration, type of patent, and a declaration worded as required by 21 C.F.R. § 314.53(c)(2): "Patent No. 6,150,365 covers the formulation, composition, and/or method of use of BuSpar®." (See attached copy of the '365 patent information submission.)

After patent information is submitted, FDA ministerially publishes it, as the Agency is specifically required to do by statute: "Upon the submission of patent information under this subsection, the Secretary shall publish it." Federal Food, Drug, and Cosmetic Act, Section 505(c)(2). FDA's publication of submitted patent information is frequently referred to as a "listing," as the Agency collates all received patent information into a list published in the Orange Book, known officially as "Approved Drug Products With Therapeutic Equivalence Evaluations." Thus, in compliance with the statute, upon submission of the '365 patent information, FDA published, or "listed," the '365 patent.

FDA's regulations provide a procedure for interested persons to dispute the accuracy or relevance of patent listings. Such persons:

> must first notify the agency in writing stating the grounds for disagreement. . . . The agency will then request of the applicable new drug application holder that the correctness of the patent information . . . be confirmed. Unless the application holder withdraws or amends its patent information in response to FDA's request, the agency will not change the patent information in the list. If the new drug application holder does not change the patent information submitted to FDA, . . . an abbreviated new drug application under section 505(j) of the act submitted for a drug that is claimed by a patent for which information has been submitted must, despite any disagreement as to

the correctness of the patent information, contain an appropriate certification for each listed patent.

21 C.F.R. § 314.53(f).

In response to FDA's request, BMS hereby confirms the correctness of the patent information it submitted on the '365 patent on November 21, 2000. Because BMS has not changed the '365 patent information it submitted to FDA, ANDAs for buspirone hydrochloride "must, despite any disagreement as to the correctness of the patent information, contain an appropriate certification" to the '365 patent. Id.

II. The Additional Declaration Requested By FDA

Based on FDA's legal analysis of the interaction of federal patent case law with a BMS press release (both supplied by buspirone ANDA applicants), the Agency asks BMS for a new declaration regarding the '365 patent. This new declaration is in addition to the declaration submitted by BMS on November 21, 2000, and goes beyond the simple confirmation requested in the regulation cited above. Specifically, FDA asks BMS to submit "a declaration that the '365 patent issued by the PTO on November 21, 2000 contains a claim for an approved use of buspirone hydrochloride that is separate from the claim for 6-hydroxy-buspirone described in the November 21, 2000 Bristol-Myers Squibb Press Release." November 30, 2000 letter from Ralph Lillie, FDA to Michael S. Eison, Ph.D., BMS (FDA Letter), at 2. BMS has done so in the attached Declaration.

The '365 patent does not simply claim a method of using 6-hydroxy-buspirone, but also claims a method of using buspirone hydrochloride. More specifically, the sole claim in the issued patent states as follows:

> A process for ameliorating an undesirable anxiety state in a mammal comprising systemic administration to the mammal of an effective but non-toxic anxiolytic dose of [6-hydroxy-buspirone] or a pharmaceutically acceptable acid addition salt or hydrate thereof.

'365 patent, column 16, lines 27-32 (emphasis added). The '365 patent claims at least two (2) ways to systemically administer 6-hydroxy-buspirone to treat anxiety: i.e., (i) direct administration of 6-hydroxy-buspirone per se, and (ii) oral administration of a prodrug such as buspirone hydrochloride.

Although the word buspirone or its chemical formula is not literally recited in this claim, well-established rules for claim construction mandated by the Supreme Court in Markman v. Westview Instruments, Inc., 116 S. Ct. 1384 (1996), require that the phrase "systemic administration" appearing in the claim be construed in view of the disclosure in the specification of the '365 patent. The specification teaches in several places that systemic administration specifically includes the oral administration of buspirone. For example, the specification teaches at Col. 11, line 64 to Col. 12, line 5, as follows:

> Systemic administration may also be realized by a second method of achieving effective anxiolytic blood levels of BMY 28674 which is to orally administer a precursor form of BMY 28674. Such prodrug forms would be administered in dosage amounts that would produce effective anxiolytic effects without causing harmful or untoward side-effects. That is, systemic administration of BMY 28674 may be accomplished by oral administration of a precursor or prodrug form of BMY 28674, e.g., buspirone, to mammals.[2]

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[2] BMY 28674 is 6-hydroxy-buspirone.

Therefore, although the claim uses the short-hand phrase "systemic administration", this claim, as a matter of law, must be construed to claim a method for ameliorating an undesirable anxiety state in a mammal comprising the direct administration of 6-hydroxy-buspirone or the oral administration of a prodrug, such as buspirone hydrochloride to provide an effective but non-toxic anxiolytic dose of 6-hydroxy-buspirone. Thus, the '365 patent claims the administration of buspirone hydrochloride for treatment of the anxiety indications for which BuSpar® has been approved.

The BMS press release was a shorthand, layperson's version of this analysis. Consequently, the statements made in the press release do not constitute a complete description of what is claimed in the '365 patent. It is of course the words of the patent itself, not the November 21, 2000 BMS press release, which define the legal scope of the '365 patent. As such, there can be no question that the '365 patent claims an approved use of buspirone hydrochloride.

III. The Inapplicability of Hoechst v. Lehman

Your letter indicates that the Hoechst case brought to your attention by buspirone ANDA applicants "suggest[s]" that "a patent on a metabolite does not meet the statutory requirements for listing in the Orange Book for the approved drug." FDA Letter at 2. Hoechst, however, is inapposite, because the '365 patent is not a metabolite patent like that at issue in Hoechst. Instead, as the attached declaration and analysis above make clear, the '365 patent claim encompasses the "oral administration of a precursor or prodrug form of BMY 28674, e.g. buspirone." '365 patent, column 12, lines 3-5. The patent at issue in Hoechst contained no similar language. Thus, the Hoechst case is irrelevant here for at least the reason that the '365 patent explicitly encompasses the administration of buspirone.

Conclusion

We hope that this submission clarifies the issues and has provided the information sought by the FDA. Please contact the undersigned should there be any questions in this regard.

Sincerely,

/s/

Matthew D. Peterson
FoxKiser
Counsel to Bristol-Myers Squibb Company

attachments

cc: Gary Buehler, Office of Generic Drugs, FDA (via facsimile)
Elizabeth Dickinson, Office of Chief Counsel, FDA (via facsimile)

TIME SENSITIVE PATENT INFORMATION

DECLARATION

Bristol-Myers Squibb Company declares that United States patent 6,150,365 issued by the United States Patent and Trademark Office on November 21, 2000 contains a claim for the approved uses of buspirone hydrochloride. The sole claim of United States patent 6,150,365 claims a method for ameliorating an undesirable anxiety state comprising the direct administration of 6-hydroxy-buspirone or oral administration of a prodrug of 6-hydroxy-buspirone such as buspirone hydrochloride to provide an effective but non-toxic anxiolytic dose of 6-hydroxy-buspirone.

/s/

Richard P. Ryan
Patent Counsel
Bristol-Myers Squibb Company
5 Research Parkway
Wallingford, CT 06492
203-677-6075

Letter from R. Lillie to M.S. Eison,
dated Dec. 6, 2000.

Michael S. Eison, Ph.D.
Director, Regulatory Sciences
Bristol-Myers Squibb Company
5 Research Parkway
Wallingford, CT 06492

By Fax and U.S. Mail

[December 6, 2000]

Dear Dr. Eison:

This letter is in response to your letter and submissions of December 4, 2000. By letter of November 30, 2000, FDA requested information related to U.S. Patent No. 6,150,365. This patent was submitted to the agency by Bristol-Myers Squibb on November 21, 2000, for listing in *Approved Drug Products with Therapeutic Equivalence Evaluations* (Orange Book) as a protection for BuSpar® (buspirone hydrochloride) (NDA 18-731)

The patent submission received by FDA on November 21, 2000, included a declaration that:

> "Patent No. 6,150,365 covers the formulation, composition, and/or method of use of BuSpar®. Specifically, Patent No. 6,150,365 is a method of use patent covering, among other things, a method of using BuSpar® for all of its approved indications, i.e., the management of anxiety disorders and the short-term relief of the symptoms of anxiety. This product is currently approved under section 505 of the Federal Food, Drug, and Cosmetic Act.

The agency's November 30, 2000 letter requested additional information related to the coverage of the '365 patent.

Specifically, FDA requested an additional declaration that the '365 patent issued by the Patent and Trademark Office on November 21, 2000 contains a claim for an approved use of buspirone hydrochloride that is separate from the claim for 6-hydroxy-buspirone described in the November 21, 2000 Bristol-Myers Squibb press release. FDA stated that, if the sole claim in the '365 patent is for the use of the metabolite of buspirone, FDA might not be able to list the patent for BuSpar® under the legal analysis described in the November 30, 2000 letter.

Bristol-Myers Squibb has submitted an additional Declaration to FDA stating:

> "Bristol-Myers Squibb Company declares that United States patent 6,150,365 issued by the United States Patent and Trademark Office on November 21, 2000 contains a claim for the approved uses of buspirone hydrochloride. The sole claim of United States patent 6,150,365 claims a method for ameliorating an undesirable anxiety state comprising the direct administration of 6-hydroxy-buspirone or oral administration of a prodrug of 6-hydroxy-buspirone such as buspirone hydrochloride to provide an effective but non-toxic anxiolytic dose of 6-hydroxy-buspirone."

The additional declaration asserts the '365 patent covers the use of the approved drug product, buspirone hydrochloride, and not solely use of a metabolite of the active ingredient in the approved drug. This information responds to the concerns described in the agency's November 30, 2000 letter. In light of the confirmation that the patent covers the use of the approved drug product BuSpar®, the '365 patent is deemed to have been listed in the Orange Book since November 21, 2000. The listing of the '365 patent is based solely upon Bristol-Myers Squibb's declarations stating the patent meets the requirements for

submission and listing. The agency does not make independent determinations regarding the scope and coverage of patents.

Thank you for your prompt response. If you have questions, please contact Mary Ann Holovac, Senior Drug Information Officer, Division of Data Management Systems, at (301) 827-3874.

Sincerely,

/s/

Ralph Lillie
Director
Office of Information Technology
Center for Drug Evaluation and Research

cc: Matthew Peterson, Esq., Fox Kiser
Gary Buehler, Office of Generic Drugs, FDA
Elizabeth Dickinson, Office of Chief Counsel, FDA

Compl., *Mylan Pharms., Inc. v. Shalala et al.*, (Civil Action No. 1:00 CV 02876) (RMU) (D.D.C), dated Nov. 30, 2000.

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IN THE UNITED STATES DISTRICT COURT
DISTRICT OF COLUMBIA

MYLAN PHARMACEUTICALS INC
781 Chestnut Ridge Road
Morgantown, West Virginia 26505

Plaintiff,

v.

Civil Action No.

DONNA E. SHALALA
Secretary
U.S. Department of Health and Human Services
200 Independence Ave., SW
Washington, DC 20204
and
JANE E. HENNEY, Commissioner
U.S. Food and Drug Administration
200 C Street, SW
Washington, DC 20204
and
U.S. FOOD AND DRUG ADMINISTRATION
5600 Fishers Lane
Rockville, MD 20857
and
BRISTOL-MYERS SQUIBB CO.
345 Park Avenue
New York, NY 10154

Defendants.

COMPLAINT

Plaintiff, Mylan Pharmaceuticals Inc., ("Mylan"), for its complaint against Defendants, Donna E. Shalala, in her official

capacity as Secretary, U.S. Department of Health and Human Services ("HHS"), Jane E. Henney, M.D., in her official capacity as Commissioner, Food and Drug Administration ("FDA"), and the U.S. Food and Drug Administration (collectively "Government Defendants") and Bristol-Myers Squibb Co. ("BMS"), alleges as follows:

INTRODUCTION

1. This action challenges FDA's refusal to accept Mylan's submission pursuant to 21 U.S.C. § 355(j)(2)(a)(viii) ("Section viii Statement"). Mylan's Section viii Statement was both authorized and required by the statute and its implementing regulations (21 C.F.R. § 314.94(a)(12)(iii)(a)). The FDA's refusal to accept Mylan's Section viii Statement is a departure from the position the FDA has taken for at least the last decade -- that it has no expertise with respect to patent-related submissions, statements, and certifications and that it will accept such submissions without looking behind those submissions to ascertain whether the patents at issue support the representations made in the submissions.

2. This action also challenges BMS' filing U.S. Patent No. 6,150,365 (the "'365 patent") with the FDA for listing in the FDA's publication Approved Drug Products with Therapeutic Equivalence Evaluations (the "Orange Book"). In filing the '365 patent with the FDA BMS misrepresented that the '365 patent covered the current approved uses of its BuSpar product. BMS made this misrepresentation with full knowledge that under its long-standing and highly publicized practice, the FDA would accept BMS' statement without question or critical analysis and list the patent in the Orange Book. This action also challenges BMS' filing of the '365 patent because, under controlling Federal Circuit precedent, the '365 patent does not "claim" a method of using the drug product BuSpar® and thus

cannot be listed in the Orange Book under 21 U.S.C. § 355(j)(2).

THE PARTIES

3. Plaintiff, Mylan Pharmaceuticals Inc., is a West Virginia corporation with its principal place of business at 781 Chestnut Ridge Road, Morgantown, West Virginia 26505-4310. Mylan is engaged in the research, development, manufacturing, and distribution of generic pharmaceutical products.

4. Defendant Donna E. Shalala is Secretary of HHS, having offices at 200 Independence Avenue, SW, Washington, DC 20204. Defendant Shalala is responsible for supervising the activities of HHS, and she is being sued in her official capacity.

5. Defendant Jane E. Henney, M.D. is Commissioner of the FDA, having offices at 200 C Street, SW, Washington, DC 20204 and 5600 Fishers Lane, Rockville, MD 20857. Defendant Henney is responsible for supervising FDA's activities, and she is being sued in her official capacity.

6. Defendant U.S. Food and Drug Administration is an agency within the Public Health Service, which is part of the U.S. Department of Health and Human Services. The FDA has offices at 5600 Fishers Lane, Rockville, MD 20857.

7. Defendant Bristol-Myers Squibb Co., is a Delaware corporation with its principal place of business at 345 Park Ave., New York, NY 10154. BMS is engaged in the research, development, manufacturing and distribution of pharmaceutical products.

JURISDICTION AND VENUE

8. This Court has jurisdiction over this action pursuant to 28 U.S.C. §1331, 5 U.S.C. §551 et seq., 28 U.S.C. §§2201-

2201 and 28 U.S.C. §1361. There exists between the parties an actual and justiciable controversy in which Mylan seeks declaratory and injunctive relief to protect its rights.

9. Venue is proper in this Court pursuant to 28 U.S.C. §1391(b) and (e).

THE HATCH-WAXMAN ACT

10. The Drug Price Competition and Patent Term Restoration Act of 1984 (Pub. L. No. 98-417) (the "Hatch-Waxman Amendments") amended the Federal Food, Drug and Cosmetic Act ("FDCA" or the "Act"). The Hatch-Waxman Amendments created §505(j) of the Act (21 U.S.C. §355(j)). Section 505(j) established the abbreviated new drug application ("ANDA") approval process, which allows low-priced generic versions of previously approved innovator drugs to be approved and brought to market on an expedited basis.

11. 21 U.S.C. §355(c)(2) provides in part that where a patent issues after a new drug application ("NDA") is approved

> the holder of an approved application shall file with the Secretary the patent number and the expiration date of any patent which claims the drug for which the application was submitted or which claims a method of using such drug and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug.

Patents so filed by an NDA-holder are listed in the Orange Book.

12. The statute requires an ANDA applicant to make certain certifications or statements to the FDA with respect to patents listed in the Orange Book. See 21 U.S.C.

§355(j)(2)(a)(vii) and (viii). In particular, 21 U.S.C. §355(j)(2)(a)(viii) requires an ANDA applicant to submit a statement:

> if with respect to the listed drug referred to in clause (i) information was filed under subsection (b) or (c) for a method of use patent which does not claim a use for which the applicant is seeking approval under this subsection, a statement that the method of use patent does not claim such a use.

If an ANDA contains a Section viii Statement, the FDA may approve the ANDA as soon as it is satisfied that the product is safe and effective.

13. The FDA has promulgated regulations implementing portions of the Hatch-Waxman Amendments. Specifically, 21 C.F.R. §314.53 covers the submission of patent information. Subsection (b) provides that "for patents that claim a method of use, the applicant shall submit information only on those patents that claim indications or other conditions of use of a pending or approved application." (Emphasis added.) 21 C.F.R. §314.94(a)(12)(iii)(A) implements the Section viii Statement providing:

> [i]f patent information was submitted under Section 505(b) or (c) of the act on §314.53 for a patent claiming a method of using the listed drug, and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent, a statement explaining that the method of use patent does not claim any of the proposed indications.

MYLAN'S ANDA AND BMS' PATENTS

14. Mylan filed an abbreviated new drug application ("ANDA"), No. 75-272, under Section 505(j) of the Federal Food, Drug and Cosmetic Act seeking approval to engage in the commercial manufacture, use and sale of its pharmaceutical formulation containing buspirone hydrochloride as a generic version of a product marketed by BMS under the trademark BuSpar®.

15. The FDA has tentatively approved Mylan's ANDA to market its buspirone hydrochloride product, evincing the Agency's determination that Mylan's ANDA meets all substantive safety and efficacy requirements. Upon information and belief, the FDA was prepared to grant final approval of Mylan's ANDA with respect to its 15 mg buspirone hydrochloride tablet (the "Mylan Buspirone Product") on November 22, 2000.

16. Upon information and belief, the only reason that the FDA has not granted final approval with respect to Mylan's Buspirone Product is that, as discussed below, on November 21, 2000, BMS filed a copy of the '365 patent with the FDA and requested its listing in the Orange Book.

17. Mylan has been and remains prepared to commence marketing, sale and shipment of its Buspirone Product immediately upon receipt of FDA final approval. Mylan has an inventory of its Buspirone Product ready for sale and has advertised the imminent availability of the product for purchase. Mylan plans to commence sale and shipment of its Buspirone Product immediately upon receipt of the FDA's final approval of Mylan's ANDA.

18. BMS has enjoyed market exclusivity with regard to buspirone since the launch of its BuSpar® product in 1986, by

virtue of two patents of which it is the assignee. United States Patent 4,182,763 ("the '763 patent") issued on January 8, 1980 and was granted two years of term extension to compensate for the lost benefit of patent term consumed by delays in regulatory approval of BuSpar®. BMS received a further six months of non-patent exclusivity under 21 U.S.C. §355(a) for submitting data to support an indication for pediatric use. The market exclusivity that BMS has enjoyed from the '763 patent expired at midnight on November 22, 2000. BMS has also been accorded market exclusivity with regard to a second patent, U.S. Patent No. 5,015,646 ("the '646 patent"), covering a specific polymorphic form of buspirone. The period of exclusivity associated with the '646 patent is due to expire on May 14, 2008.

19. The '763 and the '646 patents are both listed in the Orange Book as patents as to which a reasonable claim of patent infringement could be asserted if a person not licensed by BMS engaged in the manufacture, use or sale of its approved buspirone hydrochloride product. Because they are listed in the Orange Book, Mylan was required to file with the FDA, as part of its ANDA, certifications under 21 U.S.C. §355(j)(2)(A)(vii) with respect to the '646 and '763 patents. With respect to the '646 patent, Mylan certified under §355(j)(2)(A)(vii)(IV) that the patent would not be infringed by the commercial manufacture, use or sale of Mylan's buspirone hydrochloride product. This so-called "paragraph IV" certification, coupled with notice to the patent owner, creates an automatic stay of final approval for 45 days, after which, if no charge of infringement has been brought against the ANDA applicant by the patent owner, final approval can be granted. BMS did not sue Mylan for infringement of the '646 patent. With respect to the '763 patent, Mylan filed a certification under §355(j)(2)(A)(vii)(III), stating the date on which the patent would expire. Pursuant to this "paragraph III" certification, final approval can be granted upon the expiration of the patent.

Because BMS did not sue Mylan for infringement of the '646 patent, final approval of Mylan's ANDA should have occurred on November 22, 2000, after expiration of the '763 patent and upon expiration of all regulatory exclusivities.

20. On November 21, 2000, the United States Patent and Trademark Office issued the '365 patent, which is assigned on its face to BMS. That same day, BMS hand-delivered a request to the U.S. Food and Drug Administration that the '365 patent be listed in the Orange Book.

21. As a direct result of the listing of the '365 patent, FDA has declined to issue to Mylan the expected final approval of its ANDA.

22. On November 22, 2000, Mylan filed a letter with the FDA pursuant to 21 U.S.C. §355(j)(2)(viii) and 21 C.F.R. §314.94(a)(12)(iii)(A) stating that the '365 patent does not claim a use for which Mylan was seeking approval of its ANDA product. FDA has refused to accept Mylan's Section viii Statement, stating that it was accepting on its face BMS' gratuitous statement that the '365 patent covered all uses of BuSpar instead.

COUNT 1

23. Mylan incorporates the allegations in paragraphs 1-22 above.

24. Mylan was required by statute to submit its Section viii Statement with regard to the '365 patent.

25. The FDA has a long-standing and well-publicized practice of accepting submissions, statements, and certifications on patent-related matters on their face without looking behind those submissions to ascertain whether the patents at issue

support the representations in the submissions, statements or certifications.

26. Government Defendants' incorrectly failed to accept Mylan's statutorily required Section viii Statement and grant immediate approval of Mylan's ANDA No. 75-272, in violation of the Hatch-Waxman Amendments and pursuant to its long-standing practice.

27. Mylan requests that this Court enjoin the FDA to accept Mylan's Section viii Statement and immediately grant final approval to Mylan's ANDA No. 75-272.

COUNT 2

28. Mylan incorporates the allegations in paragraphs 1-27 above.

29. Defendant BMS' filing of the '365 patent with the FDA for listing in the Orange Book is improper and unlawful because it does not claim a method of using BuSpar with respect to which a claim of patent infringement could reasonably be asserted against an unlicensed manufacturer, user or seller of BMS's BuSpar product and because the '365 patent does not claim a method of using BuSpar. Defendant BMS' action caused the FDA improperly to deny Mylan final approval for its ANDA No. 75-272.

30. Defendant BMS' filing of the '365 patent is contrary to and in violation of the law.

31. The FDA's listing of the '365 patent and its refusal to grant final approval to Mylan's ANDA based on the listing of the '365 patent are contrary to and in violation of the law.

WHEREFORE, Mylan requests this Court

(i) declare Defendants' actions, set forth above, are unlawful and in violation of the FDCA;

(ii) enter preliminary and permanent injunctive relief against Government Defendants, ordering them to accept Mylan's Section viii Statement; ordering them not to list the '365 patent in the Orange Book; and enjoining them from continuing to refuse approval of Mylan's ANDA No. 75-272 based on BMS' filing of the '365 patent with the FDA;

(iii) enter preliminary and permanent injunctive relief against Defendant BMS ordering it to rescind its filing of the '365 patent with the FDA and ordering it to request the FDA to delist the '365 patent from the Orange Book.

Mylan further requests that the Court award Mylan its costs and attorney's fees in this action and such other relief as the Court deems just and proper.

Dated: November 30, 2000

Respectfully submitted,

By: /s/

E. Anthony Figg, D.C. Bar # 345,124
Steven Lieberman, D.C. Bar # 439,783
Mark I. Bowditch, D.C. Bar # 449,834
Elizabeth A. Leff, WA Bar # 17223; D.C. Bar pending
ROTHWELL, FIGG, ERNST & MANBECK, PC
555 13th St., N.W.; Suite 701 E
Washington, DC 20004
(202) 783-6040

Of Counsel:

Roger L. Foster
Dawn J. Beto
Mylan Pharmaceuticals Inc.
781 Chestnut Ridge Road
Morgantown, WV 26505
(304) 599-2595

Order, *Mylan Pharms., Inc., v. Thompson et al.*,
(Civil Action No. 00-2876) (RMU) (D.D.C.),
dated Mar. 13, 2001.

UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

MYLAN PHARMACEUTICALS, INC., Plaintiff, v. TOMMY G. THOMPSON, Secretary, United States Department of Health and Human Services, United States Food and Drug Administration, and BRISTOL-MYERS SQUIBB CO., Defendants.	Civil Action No.: 00-2876 (RMU) Document Nos.: 3, 4

ORDER

GRANTING THE PLAINTIFF'S MOTION FOR PRELIMINARY INJUNCTION

Upon consideration of the plaintiff's motion for preliminary injunction, the defendants' opposition thereto, and the entire record herein, and for the reasons stated in the Memorandum Opinion issued separately and contemporaneously with this Order,

it is this 13th day of March 2001,

ORDERED that Defendant Bristol-Myers Squibb Co. is hereby enjoined to request that Defendant FDA delist U.S. Patent No. 6,150,365 from its publication "Approved Drug Products with Therapeutic Equivalence Evaluations" (also known as the "Orange Book"), that is, Bristol is directed to request the FDA to remove its '365 patent from the Orange Book; and it is

FURTHER ORDERED that Defendant Tommy G. Thompson, the United States Food and Drug; Administration, and their agents, servants and employees grant immediate approval of Mylan's abbreviated new drug application (ANDA) No. 75-272 to market its pharmaceutical product containing buspirone hydrochloride as a generic version of BuSpar®.

SO ORDERED.

/s/

Ricardo M. Urbina
United States District Judge

Business Brief, "Mylan Laboratories Inc.: Extended Exclusivity of Drug, New Products Help Net Surge", *Wall St. J.*, May 9, 2002

The Wall Street Journal
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Thursday, May 9, 2002

Business Brief

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Mylan Laboratories Inc.: Extended Exclusivity of Drug, New Products Help Net Surge

Mylan Laboratories Inc. said fiscal fourth-quarter earnings surged 60%, helped by extended exclusivity on its antianxiety medication buspirone, new products and improved profit in its core generic-drug business. The pharmaceuticals firm reported net income of $67.3 million, or 53 cents a share, for the period ended March 31, up from $42.1 million, or 33 cents a share, a year earlier. The result was three cents more than Wall Street's expectation of 50 cents a share, according to Thomson Financial/First Call. Revenue climbed to $282.6 million from $248.6 million. The Pittsburgh concern also made plans to buy back stock, as the board approved the repurchase of as many as 10 million shares, or about 8% of its shares outstanding. As of 4 p.m. in New York Stock Exchange composite trading, Mylan shares climbed 8.4%, or $2.12, to $27.27.

Excerpt from Brief for Plaintiff-Appellee Mylan Pharmaceuticals Inc., *Mylan Pharms., Inc. v. Tommy G. Thompson et al. v. Bristol Myers Squibb Co.* (Appeal No. 01-1257) (Fed. Cir.), dated May 4, 2001.

Appeal No. 01-1257
UNITED STATES COURT OF APPEALS
FOR THE FEDERAL CIRCUIT

MYLAN PHARMACEUTICALS INC.,
Plaintiff-Appellee,

v.

TOMMY G. THOMPSON, SECRETARY OF HEALTH AND HUMAN SERVICES, BERNARD A. SCHWETZ, D.V.M., PH.D., ACTING PRINCIPAL DEPUTY COMMISSIONER, U.S. FOOD AND DRUG ADMINISTRATION, AND U.S. FOOD AND DRUG ADMINISTRATION,
Defendants-Appellees,

BRISTOL-MYERS SQUIBB CO.,
Defendant-Appellant.

APPEAL FROM THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA IN 00 CV 2876
JUDGE RICARDO M. URBINA

BRIEF FOR PLAINTIFF-APPELLEE MYLAN PHARMACEUTICALS INC.

E. ANTHONY FIGG
STEVEN LIEBERMAN
ELIZABETH A. LEFF
ROTHWELL, FIGG, ERNST & MANBECK
555 13th. St., N.W. Suite 701 E
Washington, D.C. 20004
(202) 783- 6040

Attorneys for Plaintiff-Appellee Mylan Pharmaceuticals Inc.

May 4, 2000

[Portions omitted.]

D. Mylan Has Not Brought a Claim to Enforce the FFDCA

Bristol argues that Mylan's action to delist the '365 patent from the Orange Book is a non-cognizable claim because the FFDCA does not create a private cause of action. Bristol cites 21 U.S.C. § 337(a) and seven cases to support its argument. Bristol Br. at 21. However, the statute and each of the cases upon which Bristol (and the Washington Legal Foundation) relies are inapposite because, as the District Court properly held, Mylan is not bringing a private action under the FFDCA. Rather, Mylan has asserted a claim under the patent laws which relies upon the FFDCA for the appropriate standards. [Internal cite omitted.] A review of the cases relied upon by Bristol illustrates this crucial difference. Those cases principally involve claims based on alleged violations of the health and safety provisions of the FFDCA; none involved a claim against the FDA (or any other government agency) or requested any relief as against the FDA.

Congress has preempted private causes of action to enforce the FFDCA because the FDA has the expertise to make safety and efficacy determinations. *See Sandoz Pharms. Corp. v. Richardson-Vicks, Inc.*, 902 F.2d 222, 230 (3d Cir. 1990). The FDA itself has stated that the determination of whether or not to list a patent is beyond the agency's expertise and has declined to make any determination regarding the propriety of patent listings relying instead upon the representations of NDA applicants. *See, e.g.*, 54 Fed. Reg. 28872, 28910-11 (1989). Congress could not have intended to preclude actions under the patent laws which refer to standards as to which the FDA has admitted it has no expertise and acts only in a "ministerial capacity. [Note omitted.]

[Portions omitted.]

CONCLUSION

The District Court's well-reasoned Opinion and Order should be affirmed.

Dated: May 4, 2001 Respectfully submitted,

By: /s/

E. Anthony Figg
Steven Lieberman
Elizabeth A. Leff
ROTHWELL, FIGG, ERNST
& MANBECK
555 13th St., N.W.; Suite 701E
Washington, DC 20004
(202) 783-6040